

ICS Recommendations on Clinical Trials in Lower Urinary Tract Dysfunction

1. Introduction

The ICS formed a committee to develop recommendations for clinical trials in LUTD. It had become apparent that ICS members wished to develop robust trial designs in the variety of conditions and disease, which form the subjects for research. The existing literature is of variable quality in terms of trial design and reporting of results. In preparing this report a variety of members of the committee gathered the existing advice and guidance and this appears in the bibliography at the end of the report. Existing guidance has been published by regulatory authorities such as the FDA and by groups of researchers attempting to raise the standard of both research studies and the reports of those studies.

This committee does not seek to replace the fine work already published but tries to provide a template for clinical researchers working in our particular field of interest. This ICS report should be read in conjunction with the existing ICS reports on terminology, standardisation and outcomes, as well as the documents listed in the bibliography.

2. Lower Urinary Tract Dysfunction (LUTD)

LUTD may be divided into abnormalities seen in the storage phase, the voiding phase, and post-micturition. The ICS has suggested that symptoms, signs and urodynamic observations and conditions are regarded separately although linked manifestations of various LUTD. It has to be acknowledged that a single symptom may have a number of different causes.

Clinical trials may target symptoms and have no objective criteria defining the cause of the symptoms, such as phase III trials in overactive bladder, which include patients on the basis of urgency and urge incontinence without requiring urodynamic demonstration of detrusor overactivity. Nevertheless such trials make the assumption that a specific LUTD exists and their medication, in this case antimuscarinic therapy, is targeted appropriately.

The commonest LUTDs are the storage phase abnormalities of detrusor overactivity and urodynamic stress incontinence and the voiding phase abnormalities of detrusor underactivity and bladder outlet obstruction. It is usual to consider five principle groups of patients: children, men, women, neurogenic patients, and the frail elderly.

This document will address separately, when necessary, the different patient groups and the different LUTDs.

3. Aims

- 3.1 To provide advice to investigators in order to improve the quality of all clinical trials in LUTD.
- 3.2 To define outcome end points e.g. cure, clinically relevant improvement and to define the relationships between various endpoints in different outcome domain
- 3.3 To enable every clinical trial to contribute to the clinical evidence base (levels of evidence) and to our understanding of LUTD.
- 3.4 To enable every clinical trial to contribute to patient management (grades of recommendation).
- 3.5 To help investigators in the submission process to ethics committees (IRBs).

4. Management of LUTD

This report covers trials and studies in the broad categories of patient investigation and treatment.

- 4.1 Patient investigation in LUTD
 - 4.1.1 symptoms and quality of life
 - 4.1.2 physical examination
 - 4.1.3 urodynamic testing
 - 4.1.4 other investigations
- 4.2 Treatment of LUTD
 - 4.2.1 Behavioural treatments
 - 4.2.1.1 lifestyle ventions
 - 4.2.1.2 pelvic floor muscle training
 - 4.2.1.3 bladder training
 - 4.2.2 Devices
 - 4.2.3 Pharmacotherapy
 - 4.2.3.1 oral treatments
 - 4.2.3.2 other routes e.g. intravesical installation or injection
 - 4.2.4 Minimally invasive treatment
 - 4.2.4.1 electrical stimulation e.g. SANS
 - 4.2.5 Surgical

5. Types of Clinical Trials

5.1. Introduction

The type of trial used will depend on the question(s) posed. Trials used in patient investigation studies will differ from those used for a new surgical technique which in turn will differ from trials used in the various stages of developing a drug.

Studies can be viewed in two broad categories, pragmatic (real life) and exploratory (the tightly controlled phase II drug trial)

5.2 Definitions

5.2.1 Explanatory trials

5.2.2 Pragmatic trials

5.2.3 Phased trials of new drugs

5.2.3.1 Phase I

5.2.3.2 Phase II (a) and (b)

5.2.3.3 Phase III

5.2.3.4 Phase IV (a) and (b)

5.2.4 Unblinded and blinded trials

5.2.4.1 Unblinded

5.2.4.2 Single-blind

5.2.4.3 Double-blind

5.2.5 Randomised controlled trials

5.2.5.1 Parallel arm

5.2.5.2 Crossover

5.2.6 Other trial types

5.2.6.1 Pilot study

5.2.6.2 Dose finding studies

5.2.6.3 Cohort studies

5.2.6.4 Case control studies

5.2.6.5 Case series

5.2.6.6 Proof of concept studies

5.2.6.7 Drug interaction studies

5.2.7 If trials compare two treatments they will fall into one of three categories of hypothesis

5.2.7.1 Equipose

5.2.7.2 Non-inferiority

5.2.7.3 Superiority

6. Trial Planning

Precise planning will be dependent on the investigation or LUTD to be studied, the patient group and the type of trial. However, broad categories are common to all trials. . biostatistician should be involved at the earliest stage.

- 6.1 Statement of hypothesis(es)/ research question
- 6.2 Placebo control needed?
- 6.3 Primary, co-primary and secondary outcome variables.
- 6.4 Effect size being sought, in the case of therapy trials.
- 6.5 Sample size calculation.
- 6.6 Inclusion/exclusion criteria.
- 6.7 Patient assessment in clinical trials
 - Use of validated instruments and standardised methods at baseline and after completion of treatment.
 - 6.7.1 symptoms/diaries/questionnaires
 - 6.7.2 severity scales
 - 6.7.3 quality of life scales at baseline
 - 6.7.4 global scales
 - 6.7.5 physical examination
 - 6.7.6 urodynamic technique
 - 6.7.7 pad tests
 - 6.7.8 genetic testing (ethics)
 - 6.7.9 other tests
- 6.8 Patient recruitment
 - 6.8.1 Representative for race, religion etc.
 - 6.8.2 Consent issues for children and the elderly
- 6.9 Data analysis and statistical planning
 - 6.9.1 Primary and secondary analyses planned a priori, ITT, PP.
 - 6.9.2 Information technology issues e.g. online collection of data.
 - 6.9.3 need for stratification by disease type (e.g. SUI and SUI/UUI) or disease severity?
 - 6.9.4 Need for a therapeutic index which combines efficacy with unwanted outcomes?
 - 6.9.5 Define randomisation procedures.
- 6.10 Planning trials in specific situations
 - 6.10.1 Trials of investigation techniques.
 - 6.10.2 Trials of behavioural therapies.
 - 6.10.3 Trials of devices.
 - 6.10.4 Trials of pharmaceuticals.
 - 6.10.5 Trials of minimally invasive treatments.
 - 6.10.6 Trials of surgical treatments.

Note: discuss need for placebo, sham treatment, specific outcomes, definitions of cure/response, surgeon experience, different conditions, (SUI UUI, nocturia, BOO) and different patient groups.

6.10.7 Trial registration.

7. Trial Conduct

All studies need to be conducted in accordance with the Helsinki agreement.

- 7.1 Patient log: a log should be kept of all patients who are seen and conform to the inclusion/exclusion criteria. The log allows for the assessment of bias.
- 7.2 Patient drop outs must be fully documented and as much data as possible recorded, including the reason for drop out e.g. concurrent illness, lack of efficacy or side effects.

8. Reporting Studies

All studies should be reported within a reasonable period of time, the ICS would suggest within 2 years of the last patient completing the study. The study should be reported, in full, in the peer reviewed literature or put into the public domain, for example on a drug company website. The ICS believes this is an ethical issue and that patients, when entering into a study believe that they are contributing to the body of evidence which will lead to improved patient care. To fail to publish is to violate this trust.

Both papers and abstracts should state that the ICS recommendations have been followed (except where detailed) and that other relevant guidelines have been complied with, for example CONSORT, QUORUM or MOOSE.

- 8.1 Outcomes, statement of
 - 8.1.1 Patient centred outcomes: cure, improvement, and failure should be stated with precise definitions.
 - 8.1.2 Objective outcomes should be reported with the appropriate statistical statements.
 - 8.1.3 Adverse events with definitions must be stated.
- 8.2 Reporting data.
 - 8.2.1 It should be stated when presented represents a post hoc rather than protocol determined analysis so that bias can be assessed.
 - 8.2.2 The minimum data required for subsequent inclusion into any meta analysis must be reported [note: details required]

- 8.3 'Ethical' issues. Competing interests of investigators, the precise role of any sponsoring company in the trial, and the issues of ownership of data, justification of ownership should be stated.

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[Notes: I haven't included economic analyses, as the paper is growing considerably. Would one line do? Are there any other issues we need to consider?]

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